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Distinguishing between post-trauma pituitary stalk disruption and genetic pituitary stalk interruption syndrome – case presentation and literature overview

Różnicowanie pomiędzy pourazowym przerwaniem szypuły przysadki a genetycznie uwarunkowanym zespołem przerwania szypuły przysadki – opis przypadku i przegląd piśmiennictwa

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Abstract

Introduction: The diagnosis of post-trauma pituitary stalk transection, which is often life-threatening condition, is frequently delayed. In medical literature still exist conflicting data concerning distinguishing this pathology with genetic developmental pituitary stalk interruption syndrome (PSIS).

Case presentation: We present a case of patient with post-trauma pituitary stalk transection resulting in combined life-threatening pituitary hormone deficiency (CPHD) and typical MRI picture: atrophic not visible stalk and posterior pituitary and hypotrophic anterior pituitary with most typical for this disorders hyperintense signal of distal regenerating axon of hypothalamus (pseudo posterior lobe) at median eminence with not visible posterior pituitary. This latter finding is often confused with ectopic posterior lobe in genetically determined PSIS.

Conclusions: MRI image together with medical history of the head trauma and its strict temporal relation with transient diabetes insipidus and the occurrence of CPHD signs, as well as the lack of extrapituitary midline defects differentiate posttraumatic pituitary stalk transection syndrome (PSTS) from genetic PSIS. In every case of severe traumatic head injury hormonal evaluation and MRI of hypothalamic-pituitary axis should be performed.

Key words:
combined pituitary hormone deficiency (CPHD), pituitary stalk interruption syndrome (PSIS), post trauma pituitary stalk disruption (PSTS), MRI.

Streszczenie

Wstęp: Rozpoznanie pourazowego przerwanie szypuły przysadki, będącego stanem zagrożenia życia, jest często opóźnione. W literaturze można znaleźć nieścisłe informacje dotyczące różnicowania tego stanu z genetycznie uwarunkowanym zespołem przerwania szypuły przysadki (*pituitary stalk interruption syndrome* – PSIS).

Opis przypadku: Przedstawiono przypadek pacjentki z pourazowym przerwaniem szypuły przysadki skutkującym wielohormonalną niedoczynnością przysadki (*combined life-threatening pituitary hormone deficiency* – CPHD) i typowym obrazem w rezonansie magnetycznym (*magnetic resonance imaging* – MRI): atroficznymi, niewidocznymi szypułą i płatem tylnym przysadki oraz hipotroficznym płatem przednim oraz – najbardziej charakterystycznym dla tego zaburzenia – hiperintensywnym sygnałem dystalnego regenerującego aksonu podwzgórza (pseudo płat tylny) w miejscu wyniosłości pośrodkowej. Ta ostatnia nieprawidłowość bywa często mylona z ektopowo położonym płatem tylnym widocznym w przypadku genetycznie uwarunkowanego PSIS.

Wnioski: Obraz MRI wraz z urazem głowy w wywiadzie pozostającym w związku czasowym z wystąpieniem przejściowej moczówki prostej oraz objawami wielohormonalnej niedoczynności przysadki, jak również brak pozaprzysadkowych zaburzeń linii środkowej ciała różnicuje pourazowe przerwanie szypuły przysadki (*post-traumatic pituitary stalk transection syndrome* – PSTS) i genetycznie uwarunkowany PSIS. W każdym przypadku ciężkiego urazu głowy należy dokonać oceny hormonalnej funkcji przysadki oraz MRI okolicy podwzgórzowo-przysadkowej.

Słowa kluczowe:
wielohormonalna niedoczynność przysadki, zespół przerwania szypuły przysadki (PSIS), pourazowe przerwanie szypuły przysadki (PSTS), MRI.

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Established facts and novel insights

Established facts

Pituitary stalk interruption syndrome (PSIS) is a relatively frequent cause of combined pituitary hormone insufficiency (CPHD) with a variety of clinical manifestations. There is increasing recognition that it is a genetic developmental malformation of the hypothalamo-pituitary region, and other midline structures, characterised in MRI by the triad of:

- absent or thin (aplastic or hypoplastic) pituitary stalk,
- absent or small (aplastic or hypoplastic) anterior pituitary lobe,
- absent or ectopic (undescendent) posterior pituitary lobe on the course of downward outgrowth of the neurohypophysis to the typical localization behind anterior pituitary lobe.

Novel insights

Post-traumatic pituitary stalk transection syndrome (PSTS) is a rare cause of CPHD albeit of usually severe clinical manifestation. It is an acquired consequence of head trauma followed by regenerating and regressive changes in hypothalamo-pituitary region which may mimic genetic PSIS triad in MRI, which are not accompanied by other midline defects:

- absent (transected) pituitary stalk which proximal stump is either visible as hyperintensive signal of regenerating nerve fibers of the hypothalamo-neurophyseal tract at median eminence or it is not visible when stalk is cut higher just at the median eminence level,
- small (hypothrophic) anterior pituitary lobe,
- absence (ischemic and neurotrophic atrophy) of posterior pituitary.

Introduction

Posttraumatic stalk transection syndrome (PSTS) and pituitary stalk interruption syndrome (PSIS) are still often mistaken from one another because of similar names of both syndromes and their resemblance in clinical manifestation and the MRI image of hypothalamo-pituitary region. However they are caused by entirely different processes: hypoplasia or aplasia in PSIS whilst regenerative and regressive changes in PSTS. Both disorders can manifest as life-threatening combined pituitary hormone deficiency (CPHD) and in both lack of pituitary stalk and small anterior pituitary can be found on MRI examination. Additionally hyperintense signal of distal regenerating axon of hypothalamus (pseudo posterior lobe) at median eminence, which is typical only for PSTS and often either confused with hyperintense bright spot of ectopic posterior pituitary typical for PSIS or incorrectly called so [1–5].

Moreover, based on historical data coming from research performed in the eighties and nineties of XX century some authors still claim that common etiological factor of both of these disorders can be breech delivery leading to structural hypoxic-ischemic changes in hypothalamo-pituitary region of the brain. Over the last two decades there is an increasing understanding of the genetical origin of PSIS associated with mutations of transcriptional factor genes which are responsible for developmental pathways of pituitary gland and other midline forebrain structures [6–12]. Breech presentation does not seem to be the cause of PSIS, but can be the cause of PSTS [2–3, 13, 14].

Distinguishing between PSTS and PSIS is becoming more important because of the prevalence of PSIS, which is approximately 1 per 6000 births [6, 8] and increasing amount of patients with PSTS after severe head traumas resulting from increasing amount of road traffic accidents and sport injures and greater survivability of victims. Traumatic brain injury occurrence in pediatric population is about 200–235 per 100 000 cases and pituitary stalk transection can be found in about 4% of them [15, 16]. However, diagnosis of both of these disorders is delayed because of the delay of hormonal assessment and MRI examination [17–20]. In PSTS it can be also caused by routinely performed computer tomography for imaging purpose of posttraumatic changes in the brain, which does not reveal pathologies of hypothalamo-pituitary region. Post-mortem studies confirmed that hypothalamo-pituitary damage is common after fatal traumatic brain injury, but MRI changes were confirmed in very few cases [15, 21–24].

We present typical case of PSTS and literature overview concerning important differences between MRI images, extrapituitary disorders and clinical manifestation in PSIS and PSTS. Awareness of these differences allow early diagnosing and differentiating. We also suggest the use of the term pituitary stalk transection syndrome (PSTS) for posttraumatic pituitary stalk transection and differentiate it with genetic pituitary stalk interruption syndrome (PSIS).

Case report

We present a case of 7 year and 10 months old girl who was admitted to Pediatrics Institute due to severe, symptomatic hypoglycemia during an acute episode of gastroenteritis. Hypoglycemia was not responsive to *i.v.* infusion of glucose (lowest glycemia value of 25 mg%). A girl was born at 41 weeks of uncomplicated gestation by elective cesarean section due to breech presentation, with a birth weight of 3600 g and length 58 cm. Apgar Score was 10 and after birth congenital dislocation of the right hip was diagnosed. Her family history was insignificant. She had no medical history of any serious diseases or health problems until the age of 3 years and 10 months when she was admitted to Intensive Care Unit because of severe head trauma after being hit by a swing. Computed tomography of the head revealed basilar skull fracture, cerebral edema, and subarachnoid hemorrhage. For few days she was kept in medically induced coma and treated with desmopressin because of transient diabetes insipidus (diabetes insipidus occurred on the day of the head trauma and lasted for few days).

After recovery the patient did not undergo any routine medical check-ups. On the present admission physical examination revealed skin pallor, orthostatic hypotension and short stature (< 3rd percentile, –3.33 SDS), body weight appropriate

for the height and no signs of sexual maturation (thelarche I, pubarche I according to the Tanner scale, axillary hair absent).

Results

Based on laboratory studies secondary adrenal insufficiency was confirmed: morning cortisol level was low 44.8 ng/ml (N: 50–230), ACTH – 5.3 pg/ml (N: 10–60) and remained low in glucagon stimulation test with max. level 55.5 ng/ml. Low serum sodium level (135 mmol/l, N: 135–145) was also found. Growth hormone deficiency was diagnosed (0.13 ng/ml during hypoglycemia and max. 0.49 ng/ml in two stimulation tests, N >10 ng/ml) with low IGF1 concentration (27.1 ng/ml, N: 59–297) and it was also confirmed by auxological data: growth on the 90th percentile on the growth chart respectively to mid-parental height with growth restriction since the age of 4 years, bone age delayed by 5 years when compared to chronological age. Secondary hypothyroidism (fT4 – 6.6 pmol/l, N: 10–25; fT3 – 1.8 pmol/l, N: 3.0–8.1, TSH – 2.89 uIU/ml, N: 0.3–4.0) was also confirmed. Gonadotropin levels were not checked as patient was in prepubertal age. Prolactin level checked twice was within normal range (197.9 and 185.0, N: 130–260 uIU/ml), and there were neither clinical nor laboratory symptoms of diabetes insipidus (serum osmolality 288 mOsm/kg H_2O, urine osmolality 119 mOsm/kg H_2O). MRI of the hypothalamo-pituitary region was performed commercially in Medical Diagnostic Centre VOXEL (sagittal and coronal plain T1-weighted and T2-weighted and dynamic post-contrast T1-weighted, three millimeter section thickness, 1.5 Tesla scanner) and described primarily as a developmental PSIS anomaly with absent pituitary stalk, hypoplastic anterior pituitary and ectopic posterior pituitary lobe located in the area of fourth ventricle infundibular recess, dorsally from the optic chiasm. Because of the strict temporal relation between biochemical and somatic symptoms and signs of CPHD with the brain damage confirmed in CT, MRI of hypothalamo-pituitary region was reassessed and revealed lack of the pituitary stalk with hiperintense signal of distal regenerating axon of the hypothalamus (pseudo posterior lobe), hypotrophic anterior pituitary and lack of posterior pituitary bright spot (Fig. 1). The introduction of multiple hormonal replacement therapy (hydrocortisone, L-thyroxine, human recombinant GH) caused resolution of hypotonia and hypoglycemia and normalization of the general condition and growth of the child (growth velocity 16 cm/year; Fig. 2).

Discussion

Pituitary stalk interruption syndrome and PSTS have different etiology, clinical manifestation, and are associated with different dangers for a patient and demand different medical procedures. Because of this, it is crucial to make an accurate diagnosis and start treatment without delay. Current data, mainly derived from familial cases and patients with specific morphological anomalies associated with PSIS support the view that PSIS constitutes an antenatal developmental event because of genetic aberrations [6, 9–12, 17]. Mutations of multiple known genes were confirmed in 5% of examined patients (e.g. TGIF, SHH, CDON, GPR161, PROKR2, GLI2, LHX4, OTX2, SOX3), but also other yet not defined holoprosencephaly-related genes are responsible for early fetal mal-development of midline structures, which results in hypoplasia or aplasia of pituitary stalk and anterior pituitary gland as well as results in absence or failure of the neurohypophysis to descend completely into sella turcica [6, 17, 25]. In 48% of PSIS cases extra-pituitary midline developmental malformations, especially in the central nervous system and the craniofacial structures are present (e.g. agenesis of corpus callosum, type 1 Chiari malformation, white matter heterotopia, upper incisor agenesis, nasal pyriform aperture stenosis, cleft lip and/or palate) [3, 6, 17] whilst they never occur as PSTS consequence.

Ischemic insult to the pituitary stalk and or mechanical rupture of the pituitary stalk occurring because of trauma during breech delivery had been suspected in the past as a causative mechanism of PSIS [2, 26–30]. These hypothesis were based on the increased incidence of breech delivery in patients with PSIS. However, no pathological proof has been found. Patients with PSIS do not exhibit damage to other structures sharing the same vascular supply. Both these hypothesis also do not explain the association of midline anomalies in these patients. Moreover, it seems that this relationship is reverse. Namely, as it was stated in our patients, decreased hormone secretion results

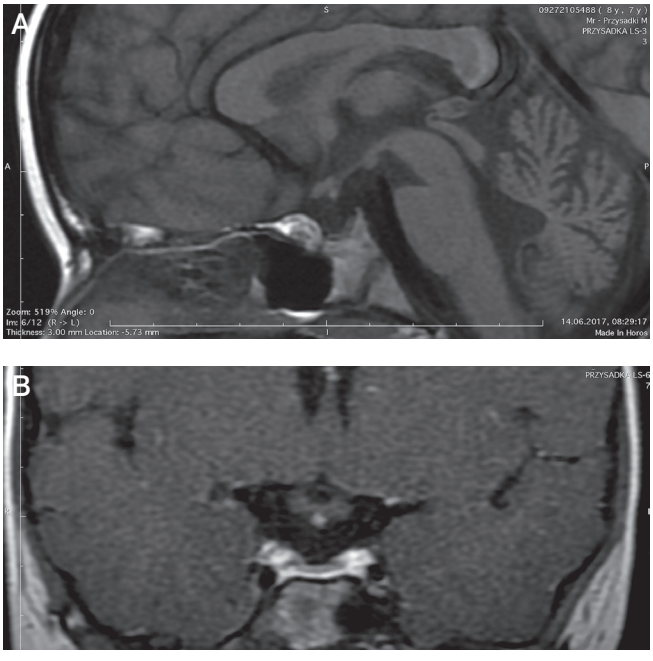

Figure 1. MRI: A) sagittal plain; small, hypotrophic anterior pituitary; B) coronal plain; hiperintense signal of distal regenerating axon of the hypothalamus (pseudo posterior lobe)

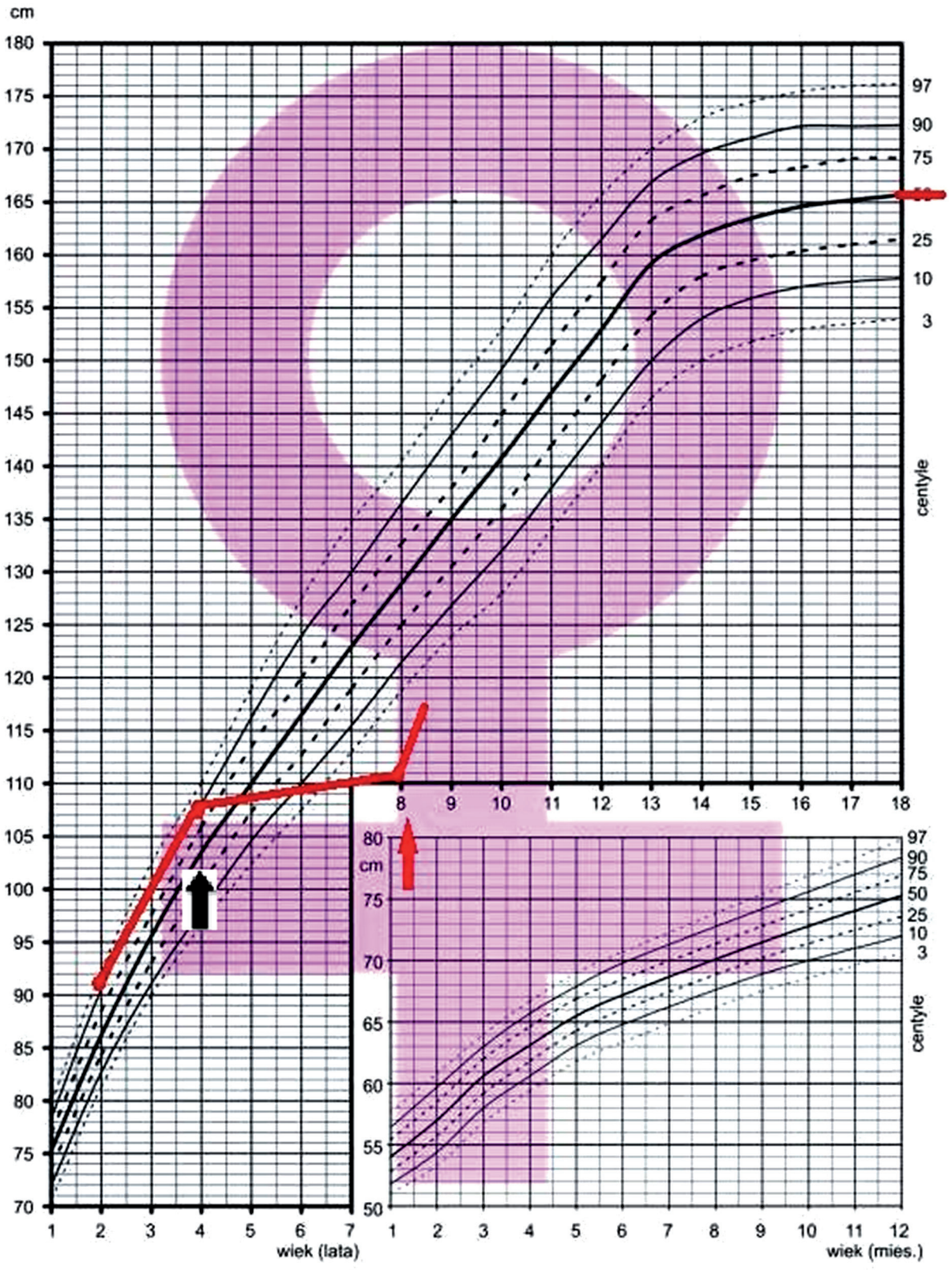

Figure 2. Growth chart of presented patient (black arrow-head trauma, red arrow-start of hormonal replacement)

in increased incidence of breech presentation which requires caesarian section in PSIS patients [3, 5, 6, 28, 31]. In addition to that, two thirds of these patients are born with no reported adverse perinatal events, with cephalic delivery in approximately 50% and caesarian section in 15% of cases, whilst breech delivery involves as much as 3% of all births and is present in only 30% of PSIS patients [31, 32]. Moreover, breech presentation and delivery cannot be the cause of extrapituitary defects.

Severe head trauma in perinatal period, but also later in life, can lead to pituitary transection and hypopituitarism in these cases, because of their etiology, should be included in PSTS [2, 13, 14, 31]. In multiple studies with both experimental animals and patients who had undergone transection of pituitary stalk hypophysectomy (therapeutic, traumatic, surgical) of adult and children etiology, anatomic changes and MRI picture in patients after pituitary stalk transection was defined [2, 33–36] .

Surgical transection of the pituitary stalk results in lack of pituitary stalk [2, 34–36]. After pituitary stalk transection anterior pituitary gland becomes small and hypotrophic because of damage of hypothalamo-hypophyseal portal system and is no longer prone to effect of regulatory hormones released by hypothalamus. Possible mechanisms of post-traumatic hypopituitarism include not only direct mechanical transection but also neuroinflammation and vascular mechanism of injury as anatomy of pituitary gland makes it vulnerable to perfusion impairment and infarction [37, 38]. The most characteristic for pituitary transection is regeneration and regrowth of the nerve fibers of the hypothalamo-neurophyseal tract and newly formed of pseudo-posterior pituitary lobe tissue at the proximal stump of the transected stalk [33–35]. Location of this pseudo-posterior pituitary depends on the level at which the stalk was sectioned [36]. If cut close to the hypothalamus, no ectopic posterior lobe develops. Such location of transected infundibulum is logical, as the median eminence (a small swelling on the tuber cinereum of the hypothalamus) is attached to the infundibulum (pituitary stalk) which ends in the pituitary. As above, MRI in our patient shows typical picture of pituitary stalk transection with no visible pituitary stalk and present infundibulum stump in the median eminence location visible as a hyperintense signal of distal axon of hypothalamus. There was hypothrophy of anterior lobe and atrophy (lack) of posterior lobe observed.

Hiperintense signal of distal axon located in proximal stalk stump has been reported in a series of PSTS children described by Fujisawa *et al.* (1987; 9 patients), Kikuchi *et al.* (1988; 12 patients), Kulkarni *et al.* (2012; 5 patients), Ergul *et al.* (2017; 1 patient) and was also presented by Ogilvy-Stuart in 2006 as typical in all newborns with CPHD due to perinatal trauma, however this structure have been named in a variety of ways e.g. "Pseudo-posterior lobe" [14], "Ectopic posterior pituitary bright spot", "Ectopic neurohypophysis", "Regeneration of the distal axon of the hypothalamus, en ectopic, superior pituitary gland", "Blunt ending of infundibulum" or improperly just "Ectopic posterior lobe", as its brightness may mimic this of posterior lobe [2, 3, 6, 13, 14, 39]. On the basis of clinical observations it is suggested that the bright spot is formed of ADH deposits [40].

Location of bright spot (of regenerating neuron in PSTS and ectopic posterior pituitary in PSIS), which signal intensity is the highest in brain tissue, may differentiate these two conditions. In large groups of patients with genetically determined PSIS (> 50 patients) characteristic on the T1-weighted MRI imaging (T1W1) is not visible posterior pituitary either in normal dorsal portion of the sella or in ectopic position (7–21% of patients) or ectopic its location (73–100%), visible dependently of the degree of the neurohypophysis mal-descendence between hypothalamus and normal posterior pituitary location: at hypothalamus (19% of PSIS patients), at the infundibulum recess (60%) or at normal position (5%) [2, 14, 17, 27, 41–44].

To a lesser degree these pathologies can be distinguished by not visible pituitary stalk, which is typical for PSTS, whilst in larger series of 67 children with PSIS not visible pituitary stalk was found in only 6% of patients and interrupted or thin pituitary stalk was found in 81% and 13% PSTS patients, respectively [17].

The size of anterior pituitary lobe is decreased in most cases and it does not allow distinguishing between PSIS and PSTS. In PSIS the size depends on mutation's severity and anterior pituitary hypoplasia can be found in 86% of patients [17]. In PSTS this anterior pituitary regression is time – dependent, as it is in the post-partum Sheehan syndrome [45]. In Ergul PSTS case, anterior pituitary was normal on MRI, but examination was done only 6 days after trauma whilst in PSTS cases diagnosed later, including our, there were anterior lobe hypothrophy [39].

In both PSTS and PSIS patients pseudo-posterior lobe or ectopic posterior lobe secret vasopressin (antidiuretic hormone – ADH), just as the genuine posterior lobe would. However, transient diabetes insipidus, which occurred in our patient, may be typical for PSTS. As it was described by Reifschneider *et al*., transient diabetes insipidus nearly always occurs early in the acute phase after head injury, contrary to the permanent diabetes insipidus, which is rare after brain injury in children [46]. In Bolado *et al*. research diabetes insipidus seems to be an indicator of poor prognosis as mortality in this group of patients is higher [47].

In both disorders (PSTS and PSIS) can occur severe symptoms of adrenal insufficiency like hypoglycemia and hyponatremia [39]. The phenotypical presentation in the neonatal period (with the exeptio hypoglycemia and hyponatremia) includes micropenis, cryptorchidism and jaundice. Hypoglycemia can also be caused by growth hormone deficiency and be accompanied with growth retardation worsened by central thyroid insufficiency and central hypogonadism resulting from gonadotropin deficiency. Our case in compliance with another current reports for PSTS typical is strict temporal relation of hormonal signs occurrence with head trauma, which caused pituitary stalk transaction, while in PSIS patients it depends upon severity of the developmental defect and progressive worsening of endocrine impairment throughout childhood and adolescence [39, 48, 49]. At diagnosis isolated growth hormone deficiency is diagnosed in 52% of the PSIS patients while CPHD in 48%, and after 12 years follow-up CPHD was confirmed in 83% patients [17].

Still recognition both disorders is significantly delayed because the age at diagnosis depends not only upon the severity of clinical manifestation but also on the clinical acuity of the caring physician and it is apparent that pertinent hormonal symptomatology was not interpreted appropriately, and therefore the underlying cause of CPHD escaped detection. Bar et al reported that out of 67 patients with PSIS, whose the median age at diagnosis was 2.5 years (range: from birth to 16.3 years of age). Severe hormonal deficiency (hypoglycemia, jaundice, micropenis, and cryptorchidism) was present in 42% of all cases and only 15% of them were diagnosed in infancy period. It should be also underline that 70% were primarily evaluated for short stature at a median age of 4 years, although decreased growth velocity and growth retardation were evident 3 and 2 years earlier, respectively [1According to some studies the diagnosis of CPHD in PSTS children is established between the first week to 16 years after head trauma [50–52]. In our case the diagnosis of hypopituitarism (GH, ACTH and TSH deficiency) was delayed for 4 years. In PSTS patients the reason of delay can be not only clinician's insufficient awareness of endocrine complications of traumatic brain injury but also routinely performing in such situations only computer tomography scan of the head, which does not reveal pathologies of hypothalamo-pituitary region. Post-mortem studies confirmed that hypothalamo-pituitary damage is common after fatal traumatic brain injury [52, 53], but MRI changes were confirmed in very few cases only [55–57].

In summary, head trauma followed by biochemical or somatic symptoms of pituitary insufficiency together with hyperintense signal of distal axon (infundibulum stump) visible in median eminence in T1-weighted MRI presentation suggest PSTS. For this disorder, lack of extrapituitary midline defects and early post-trauma development of transient diabetes insipidus are typical. In every case of severe traumatic head injury hormonal evaluation and MRI of hypothalamic-pituitary axis should be performed.

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